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SYNTHESIS OF 6-AMINOALKYLDIQUINO-1,4-THIAZINES AND THEIR ACYL AND SULFONYL DERIVATIVES[#]

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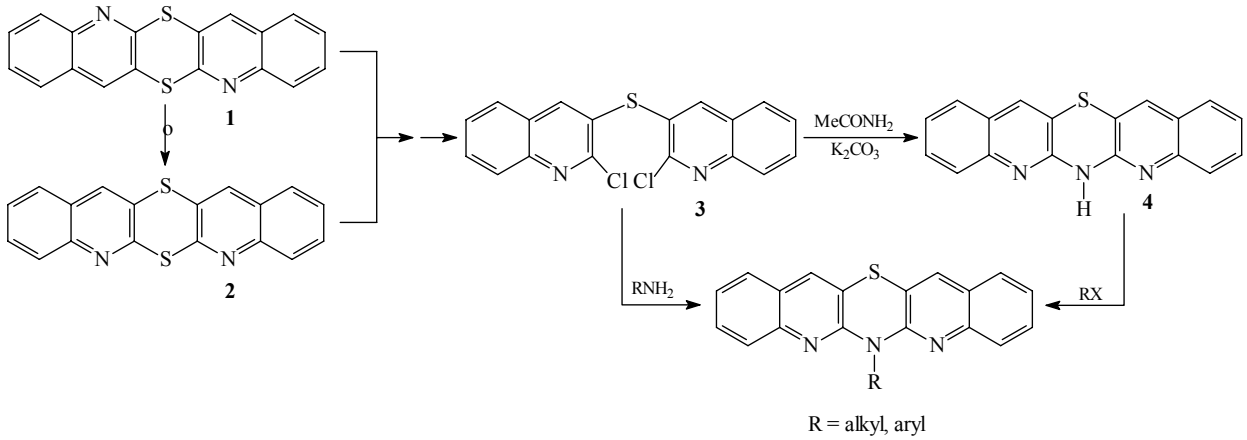
Abstract – Syntheses of various 6-dialkylaminoalkyldiquino-1,4-thiazines (**5-8**) and 6-aminoalkyldiquino-1,4-thiazines (**11-13**) were elaborated in the reactions of diquino-1,4-dithiin (**2**) and 2,2'-dichloro-3,3'-diquinolinyl sulfide (**3**) with primary amines, and 6*H*-diquino-1,4-thiazine (**4**) with dialkylaminoalkyl chlorides and phthalimidoalkyl bromides followed by hydrolysis. 6-Aminoalkyldiquino-thiazines (**11-13**) were transformed into acyl and sulfonyl derivatives (**15-26**). Some of the obtained compounds showed significant anticancer activity.

INTRODUCTION

Phenothiazines are known for varied chemical properties and very interesting biological activities (anti-psychotic, antihistaminic, antitussive and antiemetic).[1] Recent reports have focused interests on anticancer, antiplasmid and antibacterial activities, reversal of multidrug resistance and potential treatment in Alzheimer's and Creutzfeldt-Jakob diseases.[2-8] The most significant and perspective modifications of the phenothiazine structures were made by introduction of new pharmacophoric substituents at the thiazine nitrogen atom and by substitution of the benzene ring with an azine ring to form azaphenothiazines. In continuation of our search for pharmacoactive pyridine and quinoline derivatives we modified the phenothiazine structure with the quinoline ring to form new type of the linear and angular fused diquino-1,4-thiazines, being pentacyclic dibenzodiazaphenothiazines.[9-12] On the other hand, pentacyclic carbocycles and heterocycles (pentacenes and pentaphenes) are considered as a new type of electron donors[13-17] and show the significant conductive[18] and photoelectric properties[19] and constitute the active layer in a field-effect transistor device.[20]

In our previous papers[11,12] we found isomeric diquino-1,4-dithiins (**1**) and (**2**) (5,12-diaza-6,13-dithiapentacene and 5,7-diaza-6,13-dithiapentacene)[21] to be effective starting materials to synthesis of 2,2'-dichloro-3,3'-diquinolinyl sulfide (**3**) in two or three steps (in total yield of 69% or 79% from compound

(**2**), respectively). The annulation reactions of this sulfide with selected divalent reagents gave new heteropentacenes.[11] Reactions of sulfide (**3**) with acetamide, primary alkyl, aryl and heteroaryl amines led to 6*H*-diquino-1,4-thiazine (**4**) and their 6-alkyl-, aryl- and heteroaryl derivatives (Scheme 1).[12]



Scheme 1

As the most bioactive phenothiazines possess the aminoalkyl substituent attaching to the thiazine nitrogen atom, it prompted us to elaborate a synthesis of diquinothiazines with various aminoalkyl groups. In this paper, we describe the synthesis of anticancer 6-dialkylaminoalkyldiquinothiazines, 6-aminoalkyl-diquinothiazines and their selected acyl and sulfonyl derivatives.

RESULTS AND DISCUSSION

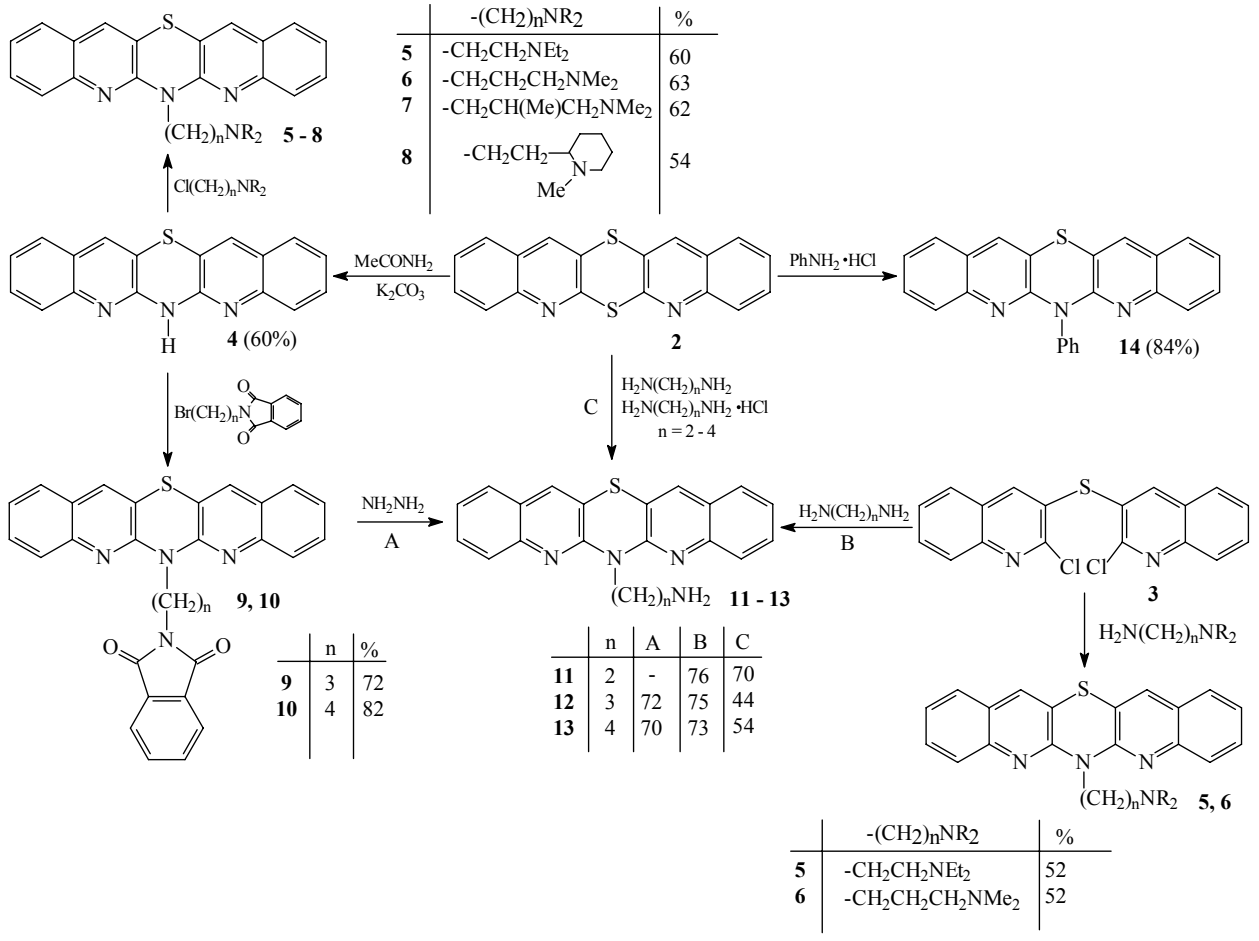
Synthesis

6-Alkyl- and aryldiquinothiazines were obtained *via* annulation reactions of sulfide (**3**) with amines or *via* *N*-alkylation and *N*-arylation of 6*H*-diquinothiazine (**4**).[12] Herein we would like to discuss the synthesis of 6*H*-diquinothiazine (**4**) and various 6-aminoalkyldiquinothiazines directly from diquino-1,4-dithiin (**2**) *via* the 1,4-dithiin ring opening and the 1,4-thiazine ring closure reactions. Diquino-1,4-dithiin (**2**) reacted with boiling acetamide (221 ^{o}C) in the presence of potassium carbonate giving 6*H*-diquinothiazine (**4**) in 60% yield (Scheme 2). An evolution of hydrogen sulfide was observed.

Since classical neuroleptic and antihistaminic phenothiazines contain the dialkylaminopropyl and dialkyl-aminoethyl chain, we transformed 6*H*-diquinothiazine (**4**) into selected 6-dialkylaminoalkyldiquinothiazines (**5-8**) in 54-63% yield in the reactions with the appropriate pharmacoactive hydrochlorides of dialkyl-aminoalkyl chlorides [2-diethylaminoethyl, 3-dimethylaminopropyl, 3-dimethylamino-2-methylpropyl and 2-(1'-methyl-2'-piperidinyl)ethyl] in refluxing dioxane in the presence of sodium hydroxide (Scheme 2). We also checked the annulation reactions of sulfide (**3**) with selected dialkylaminoalkylamines [2-(di-ethylamino)ethylamine and 3-(dimethylamino)propylamine] in boiling monomethyl ether of diethylene glycol (MEDG, 197 ^{o}C) to give 6-dialkylaminoalkyldiquinothiazines (**5**) and (**6**) in 52% yield. Motohashi and co-workers described synthesis of 10-phthalimidoalkylphenothiazines (alkyl = propyl and

butyl) from 10*H*-phenothiazine and their hydrolysis to 10-aminoalkylphenothiazines. The last compounds were transformed into selected acyl and sulfonyl derivatives. Most of them exhibited very promising anticancer and antimicrobial activity.[2-6] Analogous reactions of 6*H*-diquinothiazine (**4**) with the same phthalimidoalkyl bromides in toluene in the presence of sodium hydride gave 6-phthalimidoalkyldiquinothiazines (**9**) and (**10**) in 72% and 82% yield. Hydrolysis of compounds (**9**) and (**10**) using hydrazine led to 6-aminoalkyldiquinothiazines (**12**) and (**13**) in 89% and 70% yield (Scheme 2). Total yield of this two-step synthesis of 6-aminoalkyldiquinothiazines (**12**) and (**13**) is 64% and 57%, respectively.

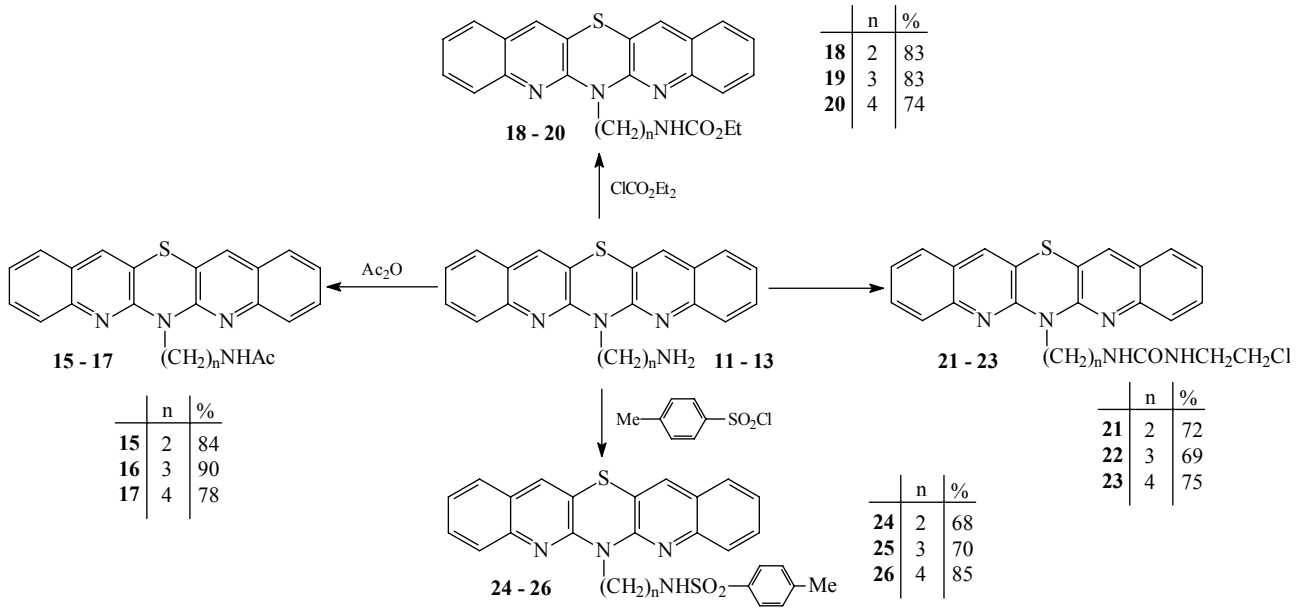
Next step was a trial of the synthesis of 6-aminoalkyldiquinothiazines (**11-13**) (alkyl = ethyl, propyl and butyl) in one step in the reaction of diquino-1,4-dithiin (**2**) with primary amine. Although a model reaction with selected amine, boiling aniline, was unsuccessful, the fusion reaction with its hydrochloride at 210 °C (without a solvent) gave 6-phenyldiquinothiazine (**14**) in 84% yield. Analogous fusion reaction with dihydrochloride of 1,2-diaminoethane was failed. Only reaction with a mixture of 1,2-diaminoethane and its dihydrochloride (1:1) in boiling MEDG led to 6-aminoethyldiquinothiazine (**11**) in 70% yield. Repeating reactions with the mixtures of other diaminoalkanes and their dihydrochlorides (1,3-diaminopropane and 1,4-diaminobutane) gave 6-aminopropyl- and 6-aminobutyldiquinothiazines (**12**) and (**13**) in 44% and 54% yields.



Scheme 2

We also checked the annulation route using sulfide (**3**) and diaminoalkanes. Reactions with 1,2-diaminoethane, 1,3-diaminopropane and 1,4-diaminobutane in boiling MEDG gave 6-aminoalkyldiquinothiazines (**11-13**) in 73-76% yield (Scheme 2). Although this process is more efficient, total efficiency of the synthesis is lesser since sulfide (**3**) is obtained from diquino-1,4-dithiin (**2**) in two or three steps.

The obtained 6-aminoalkyldiquinothiazines (**11-13**) were transformed into amide and sulfonamide derivatives. The acetylation with acetyl anhydride gave 6-acetylaminodiquinothiazines (**15-17**) in 78-90% yield. Reactions with ethyl chloroformate led to 6-ethoxycarbonylalkyldiquinothiazines (**18-20**) in 74-83% yield. Reactions with 2-chloroethyl isocyanate led to the urea derivatives possessing half-mustard unit - 6-chloroethylureidoalkyldiquinothiazines (**21-23**) in 69-75% yield. The sulfonamide derivatives were obtained in the reactions with *p*-toluenosulfonyl chloride giving 6-*p*-toluenesulfonylaminoalkyldiquinothiazines (**24-26**) in 68-85% yield (Scheme 3).



	n	%
18	2	83
19	3	83
20	4	74

	n	%
15	2	84
16	3	90
17	4	78

	n	%
21	2	72
22	3	69
23	4	75

	n	%
24	2	68
25	3	70
26	4	85

Scheme 3

Properties of 6-aminoalkyldiquinothiazines (5-26)

Syntheses of 6-aminoalkyldiquinothiazines were followed by TLC analysis as the chromatograms of the products, unlike to the chromatograms of substrates (**2**) and (**3**), showed colour changing during irradiation with UV lamp from blue to yellow. Similar yellow colour was observed when the diquinothiazine chromatograms were sprayed with a mixture detecting the phenothiazine system (sulfuric acid-water-ethanol 1:1:8).[22]

The ^{1}H NMR spectra of compound (**5-26**) showed the spectral equivalency of the left and right parts of diquinothiazine system (the C_{2v} symmetry) which is evidence that the 1,4-thiazine ring formation proceeded without the Smiles rearrangement of the S→S and S→N types. The diquinothiazine ring protons showed one singlet and four multiplets: two doublet-shaped with one *ortho*-coupling and triplet-shaped

with two *ortho*-couplings. These protons were assigned according to the methyl and phenyl (**14**) derivatives determined previously using the ^{1}H-^{1}H correlations and NOE experiments.[11] The structure of the pentacyclic ring system as 5,6,7-triaza-13-thiapentacene was confirmed by X-ray analysis of the phenyl (**14**) and *p*-nitrophenyl derivatives. The pentacene system and the thiazine ring turned out to be planar or non-planar depending on the nature of the substituent at the position 6.[12,23]

Since EI MS spectra of 6-aminoalkyldiquinothiazines (**5-26**) showed labile aminoalkyl chains, FAB MS spectra were used to determine the molecular ions.

The diquinothiazine system turned out to be more lipophilic than classical phenothiazine one.[24]

All 6-aminoalkyldiquinothiazines and their amide and sulfonamide derivatives (**5-26**) show promising potential antipsychotic, antidepressant, antihistaminic, antiasthmatic, anticancer and sedative activity[25] and some selected compounds (**5**, **6**, **15**, **16**, **19**, **21**, **24** and **25**) were tested against 57 human cancer lines in National Cancer Institute in Bethesda (USA) showing significant anticancer activities against lung, colon, breast, renal and CNS cancers, melanoma and leukemia.[26]

Conclusion

We report here synthesis of novel 6-dialkylaminoalkyldiquinothiazines, 6-aminoalkyldiquinothiazines and their amide and sulfonamide derivatives (**5-26**) *via* the annulation reactions of diquinolinyl sulfide (**3**), the dithiin ring opening - thiazine ring closure reactions of diquinodithiin (**2**) and *N*-dialkylaminoalkylation reactions of 6*H*-diquinothiazine (**4**). Some compounds show significant anticancer activities.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Boetius melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Varian Unity-Inova-300 spectrometer at 300 MHz in deuteriochloroform with tetramethylsilane as the internal standard. Electron impact (EI MS) and Fast Atom Bombardment [FAB MS, in the *m*-nitrobenzyl alcohol (nba) and glycerol (gly) matrixes] mass spectra were run on a Finnigan MAT 95 spectrometer at 70 eV. The thin layer chromatography were performed on aluminum oxide 60 F_{254} neutral (type E) (Merck 1.05581) with CH_2Cl_2 on silica gel 60 F_{254} (Merck 1.05735) with $CHCl_3$-EtOH (10:1 v/v) and as eluents.

Diquino-1,4-dithiins (**1**) and (**2**) were obtained from the reaction of 2-chloro-3-bromoquinoline with sodium sulfide according to described procedure.[21] Diquino-1,4-dithiin (**2**) was also obtained from diquino-1,4-dithiin (**1**) through the Smiles rearrangement.[21] 2,2'-Dichloro-3,3'-diquinolinyl sulfide (**3**) was obtained in the reaction of 2,2'-dimethyl-3,3'-diquinolinyl sulfide with phosphoryl chloride.[12]

Synthesis of 6*H*-diquinothiazine (4)

A mixture of diquinodithiin (**2**) (0.32 g, 1 mmole) and K_2CO_3 (0.54g, 4 mmol) was added portionally to a boiling acetamide (7.40 g, 125 mmol). Reaction was carried out for 2 h adding portionally from time to time another amount of K_2CO_3 (1.12 g, 8 mmol). After cooling water (20 mL) was added to the reaction mixture and the resulting solid was filtered off, washed with water, air-dried and crystallized from DMF to give 6*H*-diquinothiazine (**4**) (0.32 g, 60% yield); mp > 300 °C (DMF), lit.,[12] mp > 300 °C.

Synthesis of 6-dialkylaminoalkyldiquinothiazines (5-8)

A. from 6*H*-diquinothiazine (**4**)

A mixture of 6*H*-diquinothiazine (**4**) (0.30 g, 1 mmol), sodium hydroxide (0.60 g, 15 mmol) and hydrochloride of dialkylaminoalkyl chloride (3 mmol, 2-diethylaminoethyl – 0.52 g, 3-dimethylaminopropyl – 0.47 g, 3-dimethylamino-2-methylpropyl – 0.52 g, 2-(1'-methyl-2'-piperydinyl)ethyl – 0.59 g) in dry dioxane (5 mL) was refluxed for 3 h. After cooling the reaction mixture was poured into water (50 mL) and the resulted solid was filtered off washed with water, air-dried and purified by column chromatography (silica gel, $CHCl_3$-EtOH 10:1) to give:

1. 6-(2'-Diethylaminoethyl)diquinothiazine (**5**) (0.24 g, 60%); mp 144-145 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 1.76 (t, *J* = 7.2 Hz, 6H, $2CH_3$), 3.42 (q, *J* = 7.2 Hz, 4H, $2CH_2$), 3.74 (t, *J* = 7.6 Hz, 2H, CH_2), 4.99 (t, *J* = 7.6 Hz, 2H, NCH_2), 7.36 (m, 2H, H-2, H-10), 7.56 (m, 2H, H-3, H-9), 7.57 (m, 2H, H-1, H-11), 7.74 (m, 2H, H-4, H-8), 7.75 (s, 2H, H-12, H-14). FAB MS m/z: 401 (M+1, 100), 328 (M-N(C_2H_5)$_2$, 52), 301 (M+1-$CH_2CH_2N(C_2H_5)_2$, 2). Anal. Calcd for $C_{24}H_{24}N_4S$: C 71.97, H 6.04, N 13.99. Found C 71.68, H 6.01, N 13.62.

2. 6-(3'-Dimethylaminopropyl)diquinothiazine (**6**) (0.24 g, 63%); mp 110-111 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 2.40 (m, *J* = 6.9 Hz, 2H, CH_2), 2.65 (s, 6H, $2CH_3$), 3.02 (t, *J* = 6.9 Hz, 2H, CH_2), 4.72 (t, *J* = 6.9 Hz, 2H, NCH_2), 7.31 (m, 2H, H-2, H-10), 7.53 (m, 4H, H-1, H-3, H-9, H-11), 7.69 (s, 2H, H-12, H-14), 7.74 (m, 2H, H-4, H-8). FAB MS m/z: 387 (M+1, 100), 342 (M+1-$(CH_3)_2$NH, 68), 301 (M+1-$C_3H_6N(CH_3)_2$, 20). Anal. Calcd for $C_{23}H_{22}N_4S$: C 71.47, H 5.74, N 14.50. Found C 71.28, H 5.68, N 14.21.

3. 6-(3'-Dimethylamino-2'-methylpropyl)diquinothiazine (**7**) (0.25 g, 62%); mp 136-137 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 1.00 (d, *J* = 6.8 Hz, 3H, CCH_3), 2.31 (s, 6H, $2CH_3$), 2.27-2.45 (m, 2H, CCH_2), 2.52 (m, 1H, CH), 4.76 (m, 1H, NCH), 4.90 (m, 1H, NCH), 7.30 (m, 2H, H-2, H-10), 7.52 (m, 2H, H-3, H-9), 7.53 (m, 2H, H-1, H-11), 7.69 (s, 2H, H-12, H-14), 7.76 (m, 2H, H-4, H-8). FAB MS m/z: 401 (M+1, 100), 356 (M-N(CH_3)$_2$, 53), 301 (M+1-$C_4H_8N(CH_3)_2$, 38). Anal. Calcd for $C_{24}H_{24}N_4S$: C 71.97, H 6.04, N 13.99. Found C 71.62, H 6.09, N 13.69.

4. 6-(1'-Methyl-2'-piperydinylethyl)diquinothiazine (**8**) (0.23 g, 54%); mp 160-161 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 1.20-2.24 (m, 10H, $5CH_2$), 2.64 (s, 3H, CH_3), 2.99 (m, 1H, CH), 4.67 (m, 2H, NCH_2), 7.28 (m,

2H, H-2, H-10), 7.50 (m, 4H, H-1, H-3, H-9, H-11), 7.63 (s, 2H, H-12, H-14), 7.71 (m, 2H, H-4, H-8). FAB MS m/z: 427 (M+1, 56), 301 (M-$C_7H_{11}NCH_3$, 44), 154 (nba, 100). Anal. Calcd for $C_{26}H_{26}N_4S$: C 73.21, H 6.14, N 13.13. Found C 72.82, H 6.16, N 12.78.

B. from 2,2'-dichloro-3,3'-diquinolinyl sulfide (**3**)

A mixture of sulfide (**3**) (0.36 g, 1 mmol) and dialkylminoalkylamine [5 mmol, 2-(diethylamino)ethylamine – 0.70 mL, 3-(dimethylamino)propylamine – 0.64 mL] in MEDG (5 mL) was refluxed for 4 h. After cooling the reaction mixture was poured into water (50 mL) and the resulted solid was filtered off washed with water, air-dried and purified by column chromatography (silica gel, $CHCl_3$-EtOH 10:1) to give:

1. 6-(2'-Diethylaminoethyl)diquinothiazine (**5**) (0.21 g, 52%); mp 144-145 ^oC.
2. 6-(3'-Dimethylaminopropyl)diquinothiazine (**6**) (0.20 g, 52%); mp 110-111 ^oC.

Synthesis of 6-aminoalkyldiquinothiazines (11-13)

A. from 6-phthalimidoalkyldiquinothiazines (**9-10**)

To a stirred solution of 6*H*-diquinothiazine (**4**) (0.30 g, 1 mmol) in dry toluene (10 mL) NaH (0.24 g, 10 mmol, washed out with hexane) was added. The mixture was stirred for 15 min at rt, then refluxed for 15 min and a solution of *N*-(bromoalkyl)phthalimide [2 mmol, *N*-(3-bromopropyl)phthalimide – 0.54 g, *N*-(4-bromobutyl)phthalimide – 0.56 g] in toluene (5 mL) was added. The mixture was refluxed for 24 h. Next toluene was evaporated *in vaccuo* and the residue was extracted with $CHCl_3$ (2 x 5 mL)**.** The extract was concentrated and purified by column chromatography (silica gel, $CHCl_3$) to give:

1. 6-(3'-Phthalimidopropyl)diquinothiazines (**9**) (0.35 g, 72%); mp 210-211 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 2.43 (m, 2H, CH_2), 3.98 (t, J = 6.9 Hz, 2H, NCH_2), 4.83 (t, J = 6.9 Hz, 2H, NCH_2), 7.30 (m, 2H, H-2, H-10), 7.47 (m, 2H, H-3, H-9), 7.53 (m, 2H, H-1, H-11), 7.68 (s, 2H, H-12, H-14), 7.69 (m, 4H, H-4, H-8, $2H_{phthalimide}$), 7.78 (m, $2H_{phthalimide}$). FAB MS m/z: 489 (M+1, 29), 488 (M^+, 11), 301 (M+1-$C_{11}H_{10}O_2N$, 7), 154 (nba, 100). Anal. Calcd for $C_{29}H_{20}N_4O_2S$: C 71.29, H 4.13, N 11.47. Found C 70.94, H 4.12, N 11.09.

2. 6-(4'-Phthalimidobutyl)diquinothiazines (**10**) (0.41 g, 82%), mp 215-216 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 1.98 (m, 4H, $2CH_2$), 3.86 (t, J = 7.3 Hz, 2H, NCH_2), 4.71 (t, J = 7.3 Hz, 2H, NCH_2), 7.27 (m, 2H, H-2, H-10), 7.49 (m, 2H, H-3, H-9), 7.51 (m, 2H, H-1, H-11), 7.65 (s, 2H, H-12, H-14), 7.69 (m, 4H, H-4, H-8, $2H_{phthalimide}$), 7.83 (m, $2H_{phthalimide}$). FAB MS m/z: 503 (M+1, 8), 461 (M+1-C_4H_8, 32), 301 (M+1-$C_{12}H_{12}O_2N$, 2), 185 (gly, 100). Anal. Calcd for $C_{30}H_{22}N_4O_2S$: C 71.69, H 4.41, N 11.15. Found C 71.44, H 4.24, N 10.91.

Hydrolysis of 6-phthalimidoalkyldiquinothiazines (**9**) and (**10**)

To a solution of 6-phthalimidoalkyldiquinothiazines (**9**) and (**10**) (0.5 mmol) in EtOH (25 mL) 40% aqueous solution of hydrazine (0.67 mL, 6 mmol) was added. The mixture was stirred at rt for 24 h. EtOH was evaporated *in vaccuo* and the residue was extracted with $CHCl_3$ (5 mL)**.** The extract was washed with

10% ammonium hydroxide and water, and dried over Na_2SO_4. The drying agent was filtered off and filtrate was evaporated. The resulting residue was purified by column chromatography (silica gel, $CHCl_3$-EtOH 10:1) to give:

1. 6-(3'-Aminopropyl)diquinothiazine (**12**) (0.16 g, 89% yield); mp 152-153 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 2.12 (m, 2H, CH_2), 2.82 (t, *J* = 6.6 Hz, 2H, NCH_2), 4.79 (t, *J* = 6.6 Hz, 2H, NCH_2), 7.29 (m, 2H, H-2, H-10), 7.56 (m, 4H, H-1, H-3, H-9, H-11), 7.65 (s, 2H, H-12, H-14), 7.74 (m, 2H, H-4, H-8). FAB MS m/z: 359 (M+1, 14), 342 (M+1-NH_3, 11), 301 (M+1-$C_3H_6NH_2$, 6), 154 (nba, 100). Anal. Calcd for $C_{21}H_{18}N_4S$: C 70.37, H 5.06, N 15.63. Found C 70.09, H 4.98, N 15.27.

2. 6-(4'-Aminobutyl)diquinothiazine (**13**) (0.13 g, 70% yield); mp 184-185 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 1.71 (m, 2H, CH_2), 1.96 (m, 2H, CH_2), 2.89 (t, *J* = 7.0 Hz, 2H, NCH_2), 4.66 (t, *J* = 7.6 Hz, 2H, NCH_2), 7.29 (m, 2H, H-2, H-10), 7.51 (m, 4H, H-1, H-3, H-9, H-11), 7.65 (s, 2H, H-12, H-14), 7.66 (m, 2H, H-4, H-8). FAB MS m/z: 373 (M+1, 72), 356 ((M+1-NH_3, 12), 301 (M+1-$C_4H_8NH_2$, 100). Anal. Calcd for $C_{22}H_{20}N_4S$: C 70.94, H 5.41, N 15.04. Found C 70.70, H 5.49, N 14.79.

B. from 2,2'-dichloro-3,3'-diquinolinyl sulfide (**3**)

A mixture of sulfide (**3**) (0.36 g, 1 mmol) and diaminoalkane (5 mmol, 1,2-diaminoethane – 0.33 mL, 1,3-diaminopropane – 0.42 mL, 1,4-diaminobutane – 0.50 mL) in boiling MEDG (5 mL) was refluxed for 5 h. After cooling water (50 mL) was added and the resulting solid was filtered off, washed with water, air-dried and purified by column chromatography (silica gel, $CHCl_3$-EtOH 10:1) to give:

1. 6-Aminoethyldiquinothiazine (**11**) (0.26 g, 76% yield); mp 134-135 °C.

2. 6-Aminopropyldiquinothiazine (**12**) (0.27 g, 75% yield); mp 152-153 °C.

3. 6-Aminobutyldiquinothiazine (**13**) (0.27 g, 73% yield); mp 184-185 °C.

C. from diquinodithiin (**2**)

A mixture of diquinodithiin (**2**) (0.32 g, 1 mmol), diaminoalkane (2 mmol, 1,2-diaminoethane – 0.13 mL, 1,3-diaminopropane – 0.16 mL, 1,4-diaminobutane – 0.20 mL) and diaminoalkane dihydrochlorides (2 mmol, 1,2-diaminoethane dihydrochloride – 0.26 g, 1,3-diaminopropane dihydrochloride – 0.29 g, 1,4-diaminobutane dihydrochloride – 0.32 g) in MEDG (5 mL) was refluxed for 5 h. After cooling water (50 mL) was added and the resulting solid was filtered off, washed with water, air-dried and purified by column chromatography (SiO_2, $CHCl_3$-EtOH 10:1) to give:

1. 6-Aminoethyldiquinothiazine (**11**) (0.24 g, 70% yield); mp 134-135 °C. ^{1}H NMR ($CDCl_3$) δ: 3.31 (t, *J* = 6.3 Hz, 2H, NCH_2), 4.76 (t, *J* = 6.3 Hz, 2H, NCH_2), 7.30 (m, 2H, H-2, H-10), 7.52 (m, 2H, H-3, H-9), 7.55 (m, 2H, H-1, H-11), 7.68 (s, 2H, H-12, H-14), 7.76 (m, 2H, H-4, H-8). FAB MS m/z: 345 (M+1, 7), 328 (M+1-NH_3, 11), 301 (M+1-$C_2H_4NH_2$, 4), 154 (nba, 100). Anal. Calcd for $C_{20}H_{16}N_4S$: C 69.74, H 4.68, N 16.27. Found C 69.48, H 4.72, N 15.93.

2. 6-Aminopropyldiquinothiazine (**12**) (0.16 g, 44% yield); mp 152-153 °C.

3. 6-Aminobutyldiquinothiazine (**13**) (0.20 g, 54% yield); mp 184-185 °C.

Synthesis of 6-phenyldiquinothiazine (14)

Diquinodithiin (**2**) (0.32 g, 1 mmole) was mixed with aniline hydrochloride (0.26 g, 2 mmol) and the mixture was heated at 210 ^{o}C for 3 h. After cooling water (10 mL) was added to the reaction mixture and the resulting solid was filtered off, washed with water, air-dried and purified by column chromatography (Al_2O_3, CH_2Cl_2) to give: 6-phenyldiquinothiazine (**14**) (0.32 g, 84% yield); mp 262-263 ^{o}C (EtOH), lit.,[11] mp 262-263 ^{o}C.

Synthesis of 6-aminoalkyldiquinothiazines (15-17)

To a suspension of aminoalkyldiquinothiazines (**11-13**) (0.5 mmol) in pyridine (3 mL) acetic anhydride (3 mL, 32 mmol) was added and the mixture was stirred at rt for 24 h. The reaction mixture was poured into water (10 mL) and the resulting solid was filtered off, washed with water, air-dried and purified by column chromatography (silica gel, $CHCl_3$) to give:

1. 6-(2'-Acetylaminoethyl)diquinothiazine (**15**) (0.16 g, 84% yield); mp 246-247 ^{o}C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 1.39 (s, 3H, CH_3), 3.98 (m, 2H, NCH_2), 4.81 (t, J = 6.3 Hz, 2H, NCH_2), 7.34 (m, 2H, H-2, H-10), 7.59 (m, 4H, H-1, H-3, H-9, H-11), 7.71 (s, 2H, H-12, H-14), 7.75 (m, 2H, H-4, H-8). FAB MS m/z: 387 (M+1, 100), 328 (M+1-CH_3CONH_2, 46), 301 (M+1-$C_2H_4NHCOCH_3$, 11). Anal. Calcd for $C_{22}H_{18}N_4OS$: C 68.37, H 4.69, N 14.50. Found C 68.22, H 4.60 N 14.23.

2. 6-(3'-Acetylaminopropyl)diquinothiazine (**16**) (0.18 g, 90% yield); mp 285-286 ^{o}C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 2.08 (s, 3H, CH_3), 2.18 (m, 2H, CH_2), 3.43 (m, 2H, NCH_2), 4.80 (t, J = 6.6 Hz, 2H, NCH_2), 7.32 (m, 2H, H-2, H-10), 7.54 (m, 4H, H-1, H-3, H-9, H-11), 7.68 (s, 2H, H-12, H-14), 7.74 (m, 2H, H-4, H-8). FAB MS m/z: 401 (M+1, 78), 369 (M+1-CH_3OH, 26), 301 (M+1-$C_4H_6NHCOOC_2H_5$, 2), 154 (nba, 100). Anal Calcd. for $C_{23}H_{20}N_4OS$: C 68.98, H 5.03, N 13.99. Found C 68.79, H 5.09, N 13.75.

3. 6-(4'-Acetylaminobutyl)diquinothiazine (**17**) (0.16 g, 78% yield); mp 210-211 ^{o}C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 1.77 (m, 2H, CH_2), 1.95 (s, 3H, CH_3), 2.00 (m, 2H, CH_2), 3.50 (m, 2H, NCH_2), 4.68 (t, J = 7.2 Hz, 2H, NCH_2), 7.31 (m, 2H, H-2, H-10), 7.53 (m, 4H, H-1, H-3, H-9, H-11), 7.68 (s, 2H, H-12, H-14), 7.76 (m, 2H, H-4, H-8). FAB MS m/z: 415 (M+1, 100), 356 (M+1-CH_3CONH_2, 17), 301 (M+1-$C_4H_8NHCOCH_3$, 36). Anal. Calcd for $C_{24}H_{22}N_4OS$: C 69.54, H 5.35, N 13.52. Found C 69.29, H 5.37, N 13.37.

Synthesis of 6-(ethoxycarbonylaminoalkyldiquinothiazines (18-20)

To a stirred solution of aminoalkyldiquinothiazines (**11-13**) (0.5 mmol) in a mixture of CH_2Cl_2 (3 mL) and 10% Na_2CO_3 solution (3 mL), a solution of ethyl chloroformate (0.64 mL, 0.67 mmol) in CH_2Cl_2 (3 mL) was added. The mixture was stirred at rt for 24 h. The organic phase was separated and aqueous phase was extracted with CH_2Cl_2 (2 x 3 mL). The combined extracts were washed with water (2 x 5 mL)

and dried over Na_2SO_4. The drying agent was filtered off and filtrate was evaporated. The resulting residue was purified by column chromatography (silica gel, $CHCl_3$) to give:

1. 6-(2'-Ethoxycarbonylethyl)diquinothiazine (**18**) (0.17 g, 83% yield); mp 200-201 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 1.93 (t, *J* = 6.8 Hz, 3H, CH_3), 3.88 (m, 2H, NCH_2), 4.09 (q, *J* = 6.8 Hz, 2H, CH_2), 4.78 (t, *J* = 6.3 Hz, 2H, NCH_2), 7.32 (m, 2H, H-2, H-10), 7.54 (m, 4H, H-1, H-3, H-9, H-11), 7.69 (s, 2H, H-12, H-14), 7.80 (m, 2H, H-4, H-8). FAB MS m/z: 417 (M+1, 100), 328 (M+1-$NH_2COOC_2C_5$, 90), 301 (M+1-$C_2H_4NHCOOC_2H_5$, 63). Anal. Calcd for $C_{23}H_{20}N_4O_2S$: C 66.33, H 4.84, N 13.45. Found C 66.21, H 4.85, N 13.30.

2. 6-(3'-Ethoxycarbonylpropyl)diquinothiazine (**19**) (0.18 g, 83% yield); mp 183-184 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 1.33 (t, *J* = 6.8 Hz, 3H, CH_3), 2.21 (m, 2H, CH_2), 3.36 (m, 2H, NCH_2), 4.20 (q, *J* = 7.2 Hz, 2H, CH_2), 4.71 (t, *J* = 6.8 Hz, 2H, NCH_2), 7.31 (m, 2H, H-2, H-10), 7.52 (m, 4H, H-1, H-3, H-9, H-11), 7.67 (s, 2H, H-12, H-14), 7.86 (m, 2H, H-4, H-8). FAB MS m/z: 431 (M+1, 80), 369 (M+1-C_2H_5OOH, 16), 301 (M+1-$C_3H_6NHCOOC_2H_5$, 10), 154 (nba, 100). Anal. Calcd for $C_{24}H_{22}N_4O_2S$: C 66.96, H 5.15, N 13.01. Found C 66.77, H 5.11, N 12.91.

3. 6-(4'-Ethoxycarbonylbutyl)diquinothiazine (**20**) (0.17 g, 74% yield); mp 187-188 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 1.24 (t, *J* = 6.6 Hz, 3H, CH_3), 1.76 (m, 2H, CH_2), 2.00 (m, 2H, CH_2), 3.41 (m, 2H, NCH_2), 4.12 (q, *J* = 6.6 Hz, 2H, CH_2), 4.66 (t, *J* = 7.6 Hz, 2H, NCH_2), 7.30 (m, 2H, H-2, H-10), 7.51 (m, 4H, H-1, H-3, H-9, H-11), 7.67 (s, 2H, H-12, H-14), 7.79 (m, 2H, H-4, H-8). FAB MS m/z: 445 (M+1, 52), 416 (M+1-C_2H_5, 100), 301 (M+1-$C_4H_8NHCOOC_2H_5$, 2). Anal. Calcd for $C_{25}H_{24}N_4O_2S$: C 67.55, H 5.44, N 12.60. Found C 67.41, H 5.49, N 12.49.

Synthesis of 6-(chloroethylureidoalkyldiquinothiazines (21-23)

To a stirred solution of 6-aminoalkyldiquinothiazines (**11-13**) (0.5 mmol) in ethanol (25 mL) at 0 °C 2-chloroethyl isocyanate (0.08 mL, 1 mmol) was added. The mixture was stirred at 0 °C for 1h and at rt for 24 h. After evaporation of EtOH *in vaccuo* the residue was purified by column chromatography (silica gel, $CHCl_3$) to give:

1. 6-(2'-Chloroethylureidoethyl)diquinothiazine (**21**) (0.16 g, 72% yield); mp 204-205 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 3.64 (m, 4H, $2CH_2$), 3.85 (m, 2H, CH_2), 4.77 (t, *J* = 6.3 Hz, 2H, NCH_2), 7.34 (m, 2H, H-2, H-10), 7.56 (m, 4H, H-1, H-3, H-9, H-11), 7.70 (s, 2H, H-12, H-14), 7.76 (m, 2H, H-4, H-8). FAB MS m/z: 452 (M+3, 33), 451 (M+2, 25), 450 (M+1, 100), 387 (M-CH_2CH_2Cl, 11), 301 (M+1-$C_2H_4NHCONHC_2H_4Cl$, 35). Anal. Calcd for $C_{23}H_{20}ClN_5OS$: C 61.40, H 4.48, N 15.56. Found C 61.29, H 4.53, N 15.39.

2. 6-(3'-Chloroethylureidopropyl)diquinothiazine (**22**) (0.16 g, 69% yield); mp 217-218 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 2.26 (m, 2H, CH_2), 3.59 (m, 6H, $3CH_2$), 5.20 (m, 2H, CH_2), 7.53 (m, 2H, H-2, H-10), 7.65 (m, 2H, H-1, H-11), 7.73 (m, 2H, H-3, H-9), 7.92 (s, 2H, H-12, H-14), 7.96 (m, 2H, H-4, H-8). FAB

MS m/z: 466 (M+3, 13), 465 (M+2, 15), 464 (M+1, 37), 421 (M-HCNO, 17), 154 (nba, 100). Anal. Calcd for $C_{24}H_{22}ClN_5OS$: C 62.13, H 4.78, N 15.09. Found C 61.98, H 4.79, N 14.72.

3. 6-(4'-Chloroethylureidobutyl)diquinothiazine (**23**) (0.18 g, 75% yield); mp 155-156 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 2.05 (m, 4H, $2CH_2$), 3.46 (m, 2H, CH_2), 3.71 (m, 4H, $2CH_2$), 5.05 (m, 2H, CH_2), 7.56 (m, 2H, H-2, H-10), 7.59 (m, 2H, H-1, H-11), 7.68 (m, 2H, H-3, H-9), 7.76 (m, 2H, H-4, H-8), 7.98 (s, 2H, H-12, H-14). FAB MS m/z: 480 (M+3, 35), 479 (M+2, 42), 478 (M+1, 100), 415 (M-C_2H_4Cl, 12), 301 (M+1-$C_4H_8NHCONHC_2H_4Cl$, 40). Anal. Calcd for $C_{25}H_{24}ClN_5OS$: C 62.82, H 5.06, N 14.65 Found C 62.61, H 5.01, N 14.38.

Synthesis of 6-*p*-toluenesulfonylaminoalkyldiquinothiazines (24-26)

To a stirred solution of aminoalkyldiquinothiazines (**11-13**) (0.5 mmol) in a mixture of CH_2Cl_2 (3 mL) and 10% Na_2CO_3 solution (3 mL), a solution of *p*-toluenesulfonyl chloride (0.14g, 0.76 mmol) in CH_2Cl_2 (3 mL) was added. The mixture was stirred at rt for 24 h. The organic phase was separated and aqueous phase was extracted with CH_2Cl_2 (2 x 3 mL). The combined extracts were washed with water (2 x 5 mL) and dried over Na_2SO_4. The drying agent was filtered off and filtrate was evaporated. The resulting residue was purified by column chromatography (silica gel, $CHCl_3$) to give:

1. 6-(2'-*p*-Toluenesulfonylaminoethyl)diquinothiazine (**24**) (0.17 g, 68% yield); mp 228-229 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 2.11 (s, 3H, CH_3), 3.88 (t, J = 6.3 Hz, 2H, NCH_2), 4.54 (t, J = 6.3 Hz, 2H, NCH_2), 6.56 (d, J = 7.7 Hz, 2H, C_6H_2), 7.16 (d, J = 7.7 Hz, 2H, C_6H_2), 7.37 (m, 2H, H-2, H-10), 7.60 (m, 4H, H-1, H-3, H-9, H-11), 7.64 (s, 2H, H-12, H-14), 7.78 (m, 2H, H-4, H-8). FAB MS m/z: 499 (M+1, 100), 328 (M+1-$NH_2SO_2C_6H_4CH_3$, 10), 301 (M+1- $C_2H_4NH_2SO_2C_6H_4CH_3$, 10). Anal. Calcd for $C_{27}H_{22}N_4O_2S_2$: C 65.04, H 4.45, N 11.24. Found C 64.84, H 4.49, N 11.02.

2. 6-(3'-*p*-Toluenesulfonylaminopropyl)diquinothiazine (**25**) (0.18 g, 70% yield); mp 166-167 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 2.22 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 3.11 (t, J = 6.3 Hz, 2H, NCH_2), 4.72 (t, J = 7.2 Hz, 2H, NCH_2), 7.25 (d, J = 8.1 Hz, 2H, C_6H_2), 7.36 (m, 2H, H-2, H-10), 7.54 (d, J = 8.1 Hz, 2H, C_6H_2), 7.60 (m, 4H, H-1, H-3, H-9, H-11), 7.69 (s, 2H, H-12, H-14), 8.02 (m, 2H, H-4, H-8). FAB MS m/z: 513 (M+1, 100), 342 (M-$NHSO_2C_6H_4CH_3$, 10), 301 (M+1-$C_3H_6NHSO_2C_6H_4CH_3$, 25). Anal. Calcd for $C_{28}H_{24}N_4O_2S_2$: C 65.60, H 4.72, N 10.93. Found C 65.39, H 4.66, N 10.87.

3. 6-(4'-*p*-Toluenesulfonylaminobutyl)diquinothiazine (**26**) (0.23 g, 85% yield); mp 165-166 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 1.71 (m, 2H, CH_2), 1.92 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 3.20 (t, J = 6.6 Hz, 2H, NCH_2), 4.55 (t, J = 7.2 Hz, 2H, NCH_2), 7.25 (d, J = 7.9 Hz, 2H, C_6H_2), 7.30 (m, 2H, H-2, H-10), 7.52 (m, 4H, H-1, H-3, H-9, H-11), 7.64 (s, 2H, H-12, H-14), 7.76 (m, 4H, H-4, H-8, C_6H_2). FAB MS m/z: 527 (M+1, 97), 391 (M+1-$C_4H_8NHSO_2$, 100), 301 (M+1-$C_4H_8NHSO_2C_6H_4CH_3$, 7). Anal. Calcd for $C_{29}H_{26}N_4O_2S_2$: C 66.14, H 4.98, N 10.64. Found C 66.01, H 4.96, N 10.55.

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